

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person* <b>CROOKE STANLEY T</b> (Last) (First) (Middle) <b>C/O IONIS PHARMACEUTICALS, INC.</b> <b>2855 GAZELLE COURT</b> (Street) <b>CARLSBAD CA 92010</b> (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <b>IONIS PHARMACEUTICALS INC [ IONS ]</b>	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <b>Chairman and CEO</b>
	3. Date of Earliest Transaction (Month/Day/Year) <b>01/02/2019</b>	
4. If Amendment, Date of Original Filed (Month/Day/Year)		

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)			
				Code	V	(A)	(D)						Date Exercisable	Expiration Date	Title
Employee Stock Option (right to buy)	\$53.77	01/02/2019	01/02/2019	A		143,400		01/02/2020 <sup>(1)</sup>	01/01/2026	Common Stock	143,400	\$0	143,400	D	
Employee Stock Option (right to buy)	\$53.77	01/02/2019	01/02/2019	A		12,000		01/02/2020 <sup>(1)</sup>	01/01/2026	Common Stock	12,000	\$0	12,000	I	By wife

**Explanation of Responses:**

1. Grant of 01/02/2019 to reporting person or reporting person's wife (as indicated) of stock options under the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. 25% of the shares subject to the option vest and become exercisable on 01/02/2020. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments over the next 3 years. Following this transaction, the option was exercisable as to 0 on 01/02/2019.

**Remarks:**

/s/Patrick R. O'Neil, attorney-in-fact 01/03/2019

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 4 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

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